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| EXAMINER | |
|---|---|
| SCHLIENTZ, NATHAN W | |
| **ART UNIT** | **PAPER NUMBER** |
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| SHORTENED STATUTORY PERIOD OF RESPONSE | MAIL DATE | DELIVERY MODE |
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/624,362 | KAN ET AL. | |
| | Examiner | Art Unit | |
| | Nathan W. Schlientz | 1616 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *04 December 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *7/23/03* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Acknowledgement of Receipt*

Receipt of the Applicant's Response, which was filed 4 December 2006, in response to the Official Action dated 2 August 2006, is acknowledged.

### *Response to Amendment*

1. The amendment filed 4 December 2006 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: a molar ratio of the first phospholipid to the second phospholipid is larger than **1/20** (Specification Paragraph [0043]); docetaxel (Specification Paragraph [0055]); retinol, retinyl acylate and retinyl acetate (Specification Paragraphs [0051] and [0055]); the multiple derivatives of camptothecin (Specification Paragraphs [0054] and [0055]); and polyethylene glycol 600 mono(cholesteryl)ether sebecate and cholesteryl oleyl carbonate (Specification Paragraphs [0026] and [0050]).

2. The Applicants have amended the Specification paragraph [0043] to include the molar ratio of the first phospholipid to the second phospholipid is **1/20**, and states that support for the ratio of 1/20 is found in Tables 2, 3 and 4 (page 23, lines 10-11). However, Tables 2, 3 and 4 have the molar ratios of first to second phospholipids of

0/20, 10/0, 7/3, 1/4, 3/16, 2/3, and 3/2. Therefore, Tables 2, 3 and 4 do not provide support for the limitation of larger than **1/20**.

3. Also, the Applicants have amended the Specification paragraphs [0026], [0043], [0050], [0051], [0054], and [0055] to include the derivatives of paclitaxel, retinoic acid, camptothecin, and cholesterol. The Applicants also state that the derivatives of paclitaxel, retinoic acid, camptothecin, and cholesterol have been limited to well-known compounds (Remarks page 21, lines 10-21). However, the specification as originally filed does not provide support for the derivatives listed in the presently amended claims.

4. Applicant is required to cancel the new matter in the reply to this Office Action.

### *Status of Claims*

Claims 1-38 are pending. No claim is allowed at this time.

### *Claim Objections*

The objection of Claims 4, 6 and 24 under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim, is hereby withdrawn in light of Applicants' amendments.

### *Claim Rejections - 35 USC § 112, Second Paragraph*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

1. The examiner inadvertently did not include Claims 19 and 37 in the rejection under 35 U.S.C. 112, second paragraph, in the Official Action dated 2 August 2006. However, Claim 19 recites "cholesterol derivatives" and should therefore be included.

2. The rejection of Claims 8-11 and 26-29 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, has been withdrawn in view of Applicants' amendments wherein the recitation of derivative thereof has been removed.

3. Claims 12-19 and 30-36 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The use of the limitation "derivative thereof" in claims 12-18 and 30-36, specifically "paclitaxel and/or a derivative thereof", "retinoic acid and/or a derivative thereof", and "camptothecin and/or a derivative thereof" throughout the pending claims render the claims indefinite, as it is not clear to which compounds is the applicant claiming. The various derivatives of compounds instantly claimed lead to a plethora of compounds, the scope of which is not clear. Accordingly, the metes and bounds of the claims are not clear.

4. The rejection of Claim 21 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which

applicant regards as the invention, is hereby withdrawn in light of the Applicants' amendments.

5. Claim 37 stands rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The use of the limitation "cholesterol derivatives" in claim 37 renders the claim indefinite for similar reasons as discussed above for the use of "derivative thereof". The use of the term derivative leads to a number of possible compounds, and it is unclear to which derivative or derivatives of cholesterol the applicant intends to claim.

***Claim Rejections - 35 USC § 112, First Paragraph***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. Claims 8-12, 15, 18, 19, 26-30, 33, 36 and 37 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The recitation of docetaxel (Claims 8-11, 18, 26-29 and 36); retinol, retinyl acylate and retinyl acetate

(Claims 12, 18, 30 and 36); the multiple derivatives of camptothecin (Claims 15, 18, 33 and 36); and polyethylene glycol 600 mono(cholesteryl)ether sebecate and cholesteryl oleyl carbonate (Claims 19 and 37) are not supported by the original disclosure and are therefore considered new matter. The claims are therefore indefinite for being drawn to material that is considered new matter.

**Therefore, for the purposes of examination on the merits, Claims 1 and 21 are being construed by the examiner to not include the limitation "and a molar ratio of the first phospholipid to the second phospholipid is larger than 1/20".**

**Also, for the purposes of examination on the merits, Claims 8-12, 15, 18, 19, 26-30, 33, 36 and 37 are being construed by the examiner to not include the listed derivatives of paclitaxel, retinoic acid, camptothecin, and cholesterol.**

2. The rejection of Claims 8-11 and 26-29 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for liposomes comprising the hydrophobic substances paclitaxel, retinoic acid, and/or camptothecin, does not reasonably provide enablement for compositions comprising any derivatives of such hydrophobic substances, is hereby withdrawn in view of the Applicants' amendments wherein the recitation of derivatives thereof has been removed.

3. Claims 12-18, and 30-36 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for liposomes comprising the hydrophobic substances paclitaxel, retinoic acid, and/or camptothecin, does not

reasonably provide enablement for compositions comprising any derivatives of such hydrophobic substances. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Attention is directed to In re Wands, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing Ex parte Forman, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

1) the nature of the invention
2) the state of the prior art
3) the relative skill of those in the art
4) the predictability of the art
5) the breadth of the claims
6) the amount of direction of guidance provided
7) the presence or absence of working examples
8) the quantity of experimentation necessary

The instant specification fails to provide guidance that would allow the skilled artisan to practice the instant invention without resorting to undue experimentation, as discussed in the subsections set forth herein below.

The claimed invention relates to a liposome formulation comprised of two varying phospholipids, differing based upon their structure and phase transition temperatures, encapsulating a hydrophobic drug such as paclitaxel, retinoic acid, or camptothecin. The recitation of "derivative thereof", with regards to the hydrophobic substances paclitaxel, retinoic acid, and camptothecin, throughout the pending claims encompasses a plethora of compounds, wherein determining the toxicity and efficacy of all such compounds for *in vivo* use requires undue experimentation. The specification does not

provide guidance as to how one skilled in the art would go about selecting the polymer of choice in forming the instant compositions. Nor is guidance provided as to a specific protocol to be utilized in order to prove the efficacy of the presently claimed compositions in eliciting the desired response. Further, there are neither working examples nor teachings in the specification that enable one skilled in the art how to first identify the desired derivative, and second determine the desired drug/lipid ratio in order to practice the claimed invention. Therefore, the claims and specifications fail to adequately provide enough guidance for one skilled in the art to practice the claimed invention without necessary undue experimentation.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

1. The rejection of Claims 1-3, 5-9, 18 and 19 under 35 U.S.C. 102(b) as being anticipated by Sheih et al (Journal of Fermentation and Bioengineering, 1997), is hereby withdrawn from consideration in view of the Applicants' arguments that the phase transition temperature of DMPG is not within the claimed range of 40 °C to 74 °C.

2. Claims 1-9, 18, and 19 stand rejected to under 35 U.S.C. 102(b) as being anticipated by Straubinger et al US Patent 5,415,869.

Straubinger et al disclose a pharmaceutical formulation comprising a mixture of one or more negatively charged phospholipids and one or more zwitterion phospholipids (see claim 1). Straubinger et al further disclose the negatively charged phospholipids include dipalmitotylphosphatidyl glycerol, distearyloyl phosphatidyl glycerol, and dipalmitoylphosphatidyl serine (see claim 2). Straubinger et al further disclose the zwitterion phospholipid include dioleoylphosphatidyl choline, and dilaurloylphosphatidyl choline (see claim 3). Straubinger et al further disclose the pharmaceutical formulation with taxol (paclitaxel, see claim 6) and cholesterol (see claim 8). Therefore, Straubinger et al anticipate the instant claims.

3. Claims 1-7, 19, 21-25 and 37 stand rejected to under 35 U.S.C. 102(b) as being anticipated by Scotto et al. US Patent 4,873,089.

Scotto et al. disclose a proteoliposome formulation comprising a lipid component/phospholipid, i.e. egg or soy phosphatidycholine (EPC or SPC) and a fusogen, i.e. distearoyl phosphatidylcholine, dipalmitoylphosphatidyl choline, hydrogenated egg phosphatidylcholine or hydrogenated soy phosphatidylcholine (HEPC or HSPC) (see column 5, lines 37-64; and Claims 1, 5 and 6). Scotto et al. further disclose the fusogen to be any lipophilic molecule (column 5, lines 14-18). Thus, the fusogens disclosed by Scotto et al. are inherently hydrophobic substances. Scotto et al. further disclose the proteoliposomes comprising a saturated fatty acid, optionally

cholesterol (see example 3; and column 10, lines 24-45). Scotto et al. also disclose the association of the said formulation with a drug (see column 8, lines 11-37). Therefore, Scotto et al anticipate the instant claims.

4. Claims 1-3, 5-9, 15, 16, 18 and 19 stand rejected to under 35 U.S.C. 102(b) as being anticipated by Castor et al US Patent 5,776,486.

Castor et al disclose liposomes containing hydrophobic drugs. In particular, Castor et al. disclose liposomes comprising phosphatidylcholine (PC), phosphatidylethanolamine (PE), and soy bean phosphatidylcholine (SPC), cholesterol, and paclitaxel or camptothecin (column 23, lines 10-67; column 24, lines 14-16 and 26-28; Examples 10-14; and Claims 2, 10, 12, 13, 15, 26 and 27). Therefore, Castor anticipates the instant claims.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

1. Claims 20 and 38 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Scotto et al. US Patent 4,873,089 in view of. and Crosasso et al (Journal of Controlled Release (2000) 63, 19-30).

Scotto et al teaches liposome formulations comprising a fusogen and a phospholipid, wherein the fusogen include distearoyl phosphatidylcholine, dipalmitoylphosphatidyl choline, hydrogenated egg phosphatidyl choline or hydrogenated soy phosphatidyl choline and the phospholipids include egg or soy phosphatidylcholine (EPC or SPC) (see column 4, lines 56-64; column 5, lines 24-64; and Claims 1, 5 and 6). Scotto et al. also teach the inclusion of a lipophilic molecule that can be included in the phospholipid bilayer including cholesterol and cholesterol derivatives (column 5, lines 14-33). Scotto et al. further disclose the lipid vesicle

associated with a drug or other biologically active or physiologically active agent (see column 8, lines 11-13).

The instant claims teach liposome formulations comprising a first and second phospholipid, one or more hydrophobic substances, and the liposome-forming material MPEG-DSPE. The difference between the instant claims and Scotto et al. is that Scotto et al. doesn't teach the addition of MPEG-DSPE with the liposome formulations.

However, it is known in the art that polyethylene glycol conjugated, "PEGylated", liposomes have a longer circulation time in the bloodstream prior to being metabolized. Therefore, liposome formulations being used to carry drugs to target cells via intravenous injection benefit greatly from the addition of PEG or PEG derivatives by allowing lower dose injections because the amount of drug reaching the target cells would be increased. It is for that reason the examiner joins Crosasso et al.

Crosasso et al. teaches liposome preparations by employing hydrophilic polymer-conjugated phospholipid (methoxy polyethylene glycol-phosphatidylethanolamine) in order to enhance the liposomes circulation time in blood post iv administration. Crosasso et al. further teaches the incorporation of cholesterol within the "PEGylated" (polyethylene glycol conjugated) liposomes comprising EPC, phosphatidylglycerol (PG), and paclitaxel. However, Crosasso et al. does not teach liposomes comprising EPC or SPC and HEPC or HSPC.

Accordingly, in order to prolong the circulation in the bloodstream for the formulations of Scotto et al. it would have been obvious to one skilled in the pertinent art at the time of the invention to combine those liposome compositions with MPEG-DSPE

as in Crosasso et al. The persons skilled in the art would have had reason to expect the PEGylated liposomes comprising HEPC or HSPC and EPC or SPC, cholesterol, drug, and MPEG-DSPE would have delivered the said drug to the target cell more efficiently because of the prolonged circulation within the bloodstream.

2. Claims 1-19 and 21-37 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Scotto et al. US Patent 4,873,089 in view of Unger et al. US Patent 5,733,572, and Castor et al. US Patent 5,776,486.

Scotto et al. teachings are discussed above. Scotto et al. does not disclose the hydrophobic substances paclitaxel, retinoic acid, and camptothecin being encapsulated in their liposome formulations.

The difference between the claimed invention and the teachings of Scotto et al. resides in the encapsulation of the specific hydrophobic substances paclitaxel, camptothecin, and retinoic acid. It is known in the art that liposome-based drug formulations are able to achieve the equivalent therapeutic efficacy to free drug, as well as reduce the systemic toxicity in many applications. Because of the toxicity associated with free paclitaxel, camptothecin, and retinoic acid it would be beneficial to incorporate these drugs within the liposome formulations of Scotto to reduce the toxic side effects. It is for that reason the examiner joins Unger et al. and Castor et al.

Unger et al. discloses dipalmitoylphosphatidylcholine (DPPC) liposomes incorporating vitamin A (retinoic acid) (see example 8, column 53, line 6-15). Unger et al., however, doesn't teach liposome formulations comprising a first and a second

phospholipid, a liposome-forming material such as cholesterol, antioxidant, or PEGylated lipids.

Castor et al. discloses encapsulation of paclitaxel or camptothecin within liposomes comprising EPC and cholesterol. However, Castor et al. doesn't disclose the use of a first and second phospholipid chosen based upon their phase transition temperatures.

Accordingly, it would be obvious to one skilled in the pertinent art at the time of the invention to employ the liposomes of Scotto et al. in combination with any hydrophobic substance of Castor et al. and/or Unger et al., because the persons skilled in the art would have had a reasonable expectation of success in conventionally encapsulating a drug of choice (paclitaxel, retinoic acid, or camptothecin) within the liposomes of Scotto et al. and reducing the side effects associated with the toxicity of the drugs.

***Examiner's Response to Applicant's Remarks***

Applicant's arguments filed 4 December 2006 have been fully considered, and in some instances are found persuasive while in other instances they are found unpersuasive.

1. 35 U.S.C. 112, second paragraph, rejection of claims 8-18 and 26-37 as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

The Applicants amended the claims and therefore the rejection of Claims 8-11 and 26-29 is withdrawn. The examiner inadvertently did not include Claim 19 in the rejection, however it should be included because of the recitation of "cholesterol derivatives". The Applicants argue on page 21 that broad claim language does not mean that it is indefinite. However, the amended claims recite, "the derivatives include". The term "include" is open-ended and does not limit the scope of the claims to those listed. Therefore, the metes and bounds of the claims are still indefinite because a derivative of a compound includes any number of permutations of that compound resulting in another compound with different structure and properties. Therefore, the term derivative or derivative thereof affords a plethora of species with different structures and properties. Thus, the rejection of Claims 12-19 and 30-37 under the second paragraph of 35 U.S.C. 112 is maintained.

2. 35 U.S.C. 112, first paragraph, rejection of claims 8-18 and 26-36, because the specification, while being enabling for liposomes comprising the hydrophobic substances paclitaxel, retinoic acid, and/or camptothecin, does not reasonably provide enablement for compositions comprising any derivatives of such hydrophobic substances.

The Applicants argue on page 22 that an ordinarily skilled person in the art would be fairly knowledgeable about the art, and that the amendments along with this knowledge of the art should overcome the rejection. However, the amendments state the derivatives "include" and thus do not limit the scope of the claims to those listed.

Also, a person skilled in the art would immediately be able to identify a plethora of compounds that qualify as a derivative of paclitaxel, retinoic acid, or camptothecin, that are not adequately supported by the specification. Thus, the rejection under the first paragraph of 35 U.S.C. 112 is maintained.

3. Applicant's arguments, see page 24, line 12 through page 25, line 3, with respect to Claims 1-3, 5-9, 18 and 19 have been fully considered and are persuasive. The rejection of Claims 1-3, 5-9, 18 and 19 as being anticipated by Sheih et al. has been withdrawn.

4. 35 U.S.C. 102(b) rejection of Claims 1-9, 18 and 19 as being anticipated by Straubinger et al.

The Applicants argue that it is not necessary to use negatively charged and zwitterion phospholipids together in the claimed invention, as is disclosed by Straubinger et al. However, the disclosure of Straubinger et al. clearly lists the negatively charged phospholipids as including phosphatidyl serine, phosphatidyl glycerol, dipalmitotylphosphatidyl glycerol, distearyloylphosphatidyl glycerol, dimyristoyl phosphatic acid, dipalmitoyl phosphatic acid, and dipalmitoyl phosphatidyl serine (claim 2), which are listed as possible first phospholipids in the instant claims (Claims 3 and 4) and thus inherently meet the phase transition temperature limitations. Also, Straubinger et al. clearly lists the zwitterion phospholipids as including phosphatidyl choline, phosphatidyl ethanolamine, dioleoylphosphatidyl choline and dilauryloylphosphatidyl

choline (Claim 3), which are listed as possible second phospholipids in the instant claims (Claims 5 and 6) and thus meet the phase transition temperature limitations.

The Applicants also argue that the instantly claimed liposomes are able to incorporate a very high content of paclitaxel, such as 20 mole% paclitaxel, and remain stable for at least 60 days (page 25, lines 11-13). However, it is noted that the features upon which applicant relies are not recited in the rejected claims. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Also, Straubinger et al. clearly states the liposomes comprise at least one taxane in an amount of 1.5-8.0 mol% (Claim 1). Thus, the liposomes of Straubinger et al. are able to incorporate "high content" of taxanes, i.e. paclitaxel.

The Applicants also argue that Straubinger et al. do not disclose a drug delivery temperature and a drug storage temperature such that $T_{g1} > T_1 > T_2 > T_{g2}$. However, the examiner respectfully disagrees. Straubinger et al. disclose a storage temperature for their liposomes of 4 °C (column 12, lines 23-27), which is the same as disclosed in the Applicant's specification (page 11, lines 10 and 11). Also, Straubinger et al. disclose the use of their liposomes in oral, parenteral, or topical administration (column 10, line 37). Thus, the drug delivery temperature of the liposomes of Straubinger et al. must be the same as the drug delivery temperature of the Applicant's specification (page 11, lines 5 and 10-11). Therefore, Straubinger et al. disclose the phase transition temperature of the negatively charged phospholipid is greater than the drug delivery

temperature, which is greater than the drug storage temperature, which greater than the phase transition temperature of the zwitterion phospholipid, i.e. $T_{g1} > T_1 > T_2 > T_{g2}$.

Therefore, for aforementioned reasons, Straubinger et al. anticipate all the limitations of the instant claims.

5. 35 U.S.C. 102(b) of Claims 1-7, 19, 21-25 and 37 as being anticipated by Scotto et al.

The Applicants argue that the disclosure of Scotto et al. does not comprise a first and a second phospholipid and that they require the correct phase transition temperatures. The examiner respectfully disagrees. Claim 1 of Scotto et al. requires mixing of a fusogen with a lipid component. Claims 5 and 6 of Scotto et al. disclose the fusogen includes distearoyl phosphatidylcholine, dipalmitoylphosphatidyl choline, hydrogenated egg phosphatidylcholine or hydrogenated soy phosphatidylcholine, and the lipid component is a phospholipid including egg or soy phosphatidylcholine. Thus the fusogen and phospholipids of Scotto et al. inherently possess the proper phase transition temperatures.

The Applicants also argue that Scotto's formulation is used for incorporating proteins, and not used for incorporating hydrophobic substances. However, Scotto et al. does disclose that the fusogen is any lipophilic molecule (column 5, lines 14-18), and that the formulations may be associated with a small molecular weight drug (column 8, lines 28-33). Therefore, the formulations of Scotto et al. are incorporating a

hydrophobic substance, i.e. the fusogen, and disclose the association of the proteoliposome with a small molecular weight drug.

Therefore, for aforementioned reasons, Scotto et al. anticipate all the limitations of the instant claims.

6. 35 U.S.C. 102(b) of Claims 1-3, 5-9, 15, 16, 18 and 19 as being anticipated by Castor et al.

The Applicants argue that the Castor et al. reference does not disclose that the first and second phospholipids are required and that they are limited by the phase transition temperatures as instantly claimed. However, Castor et al. disclose the use of chicken egg yolk, which consists of PC, PE and SPC (column 23, lines 10-15), which inherently possess the phase transition temperature limitations.

The Applicants also argue that Castor et al. do not disclose the temperature relationship $T_{g1} > T_1 > T_2 > T_{g2}$. However, Castor et al. disclose the storage temperature of the liposomes to be 4 °C (column 31, line 7), and the liposomes are intraperitoneally administered (column 32, line 57). Therefore, the $T_{g1} > T_1 > T_2 > T_{g2}$ relationship is anticipated by Castor et al.

Therefore, for the aforementioned reasons, Castor et al. anticipate all the limitations of the instant claims.

7. 35 U.S.C. 102(b) of Claims 20 and 38 as being unpatentable over Scotto et al. in view of Crosasso et al.

The Applicants argue that none of the teachings suggest the liposome formulations require the phase transition temperature limitations and the drug delivery and drug storage temperature limitations (page 27, lines 14-24). However, Scotto et al. teach mixing a fusogen with a lipid component, wherein the fusogen is selected from distearoyl phosphatidylcholine, dipalitoylphosphatidyl choline, hydrogenated egg phosphatidyl choline or hydrogenated soy phosphatidyl choline, and the lipid component is selected from egg or soy phosphatidyl choline (Claims 1, 5 and 6). Scotto et al. also teach a proteoliposome consisting of EPC, DMPC, DPPC, and DSPC (column 10, Example 3). Therefore, the phospholipids of Scotto et al. inherently possess the requisite phase transition temperatures. Scotto et al. further teach the proteoliposomes as a medicament that can be administered through intravenous injection (column 8, lines 55-56). Therefore, the drug delivery temperature of the proteoliposomes of Scotto et al. are meet the requisite relationship of being below that of the first phospholipid, i.e. DPPC, DSPC, HEPC, and HSPC, and above that of the second phospholipid, i.e. EPC. Also, Scotto et al. teach the proteoliposomes are maintained at a temperature at or below the phase transition temperature, such as 0-37 °C (column 7, lines 25-26 and 43-50). Therefore, the proteoliposomes of Scotto et al. meet the phase transition temperature, drug delivery temperature, and drug storage temperature limitations.

The Applicants also argue the examiner used hindsight reconstruction to pick or choose among isolated disclosures in the prior art to deprecate the claimed invention

(page 28, lines 1-5). In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

The teachings of Crossasso et al. are incorporated in order to show the desire and benefit of employing hydrophilic polymer-conjugated phospholipid in order to enhance the liposomes circulation time in the blood post iv administration.

Therefore, for the aforementioned reasons, the instant claims are unpatentable over Scotto et al. in view of Crossasso et al.

8. 35 U.S.C. 102(b) of Claims 1-19 and 21-37 as being unpatentable over Scotto et al. in view of Unger et al. and Castor et al.

The Applicants argue that none of the teachings suggest the liposome formulations require the phase transition temperature limitations and the drug delivery and drug storage temperature limitations (page 27, lines 14-24). However, the teachings of Scotto et al. are discussed above, which teach proteoliposomes that are made of a first and second phospholipid, and meet the phase transition temperature,

drug delivery temperature, and drug storage temperature limitations set forth in the instant claims.

The Applicants also argue the examiner used hindsight reconstruction to pick or choose among isolated disclosures in the prior art to deprecate the claimed invention (page 28, lines 1-5). In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

The teachings of Unger et al. and Castor et al. are relied upon to show the desire and expectation of success for incorporating retinoic acid, paclitaxel, or camptothecin in a liposome formulation.

Therefore, for the aforementioned reasons, the instant claims are unpatentable over Scotto et al. in view of Unger et al. and Castor et al.

***Conclusions***

9. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

***Contact Information***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nathan W. Schlientz whose telephone number is 571-272-9924. The examiner can normally be reached on 8:30 AM to 5:00 PM, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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